Clinical Endpoint Bioequivalence Studies for Locally Acting Drugs

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Bioequivalence studies for Locally Acting Drugs
Clinical Endpoint **Bioequivalence** Studies for Locally Acting Drugs. Dena R. **Hixon**, MD. Associate ...
http://www.fda.gov/ohrms/dockets/ac/03/slides/3926S1_18_Hixon.ppt - Cached -

Systemic Drugs

- Delivered to the bloodstream for distribution to site(s) of action in the body
- BE determined with PK studies
  - Relatively short studies
  - Relatively little variability in results
  - Relatively small number of subjects

Locally-Acting Drugs

- Not intended to be absorbed into the bloodstream
- Delivered directly to sites of action in the skin, mouth, eyes, ears, nose, vagina, urinary tract, or gastrointestinal tract

Locally-Acting Drugs

- Topical acne creams, lotions, or gels
- Topical or vaginal antifungal creams or suppositories
- Oral lozenges for oral candidiasis
- Ophthalmic drops for conjunctivitis
- Otic drops for external otitis
- Oral vancomycin for pseudomembranous colitis
- Nasal sprays for rhinitis
- Orally inhaled products for asthma

BE of locally-acting drugs

- PK studies are not adequate
- Pharmacodynamic (PD) studies for topical steroids
- Most require clinical endpoint studies
- Combination products may require both PD and clinical endpoint studies

Clinical endpoint studies

- 3-arm comparative trials of generic vs. reference listed drug (RLD) vs. placebo
- Treatment of an approved indication in a patient population according to the labeled dosing of the RLD.
- Trial design and endpoints similar to NDA

Clinical endpoint studies

- Both generic and RLD must be statistically superior to placebo ($p<0.05$) in order to assure that the study is sensitive enough to show a difference between products.
- Same established BE requirements as for other types of BE studies

Challenges of clinical endpoint studies

- Clinical endpoints more variable than PK but must meet the established BE limits
- May require several hundred patients
- Study duration may be several weeks depending upon the approved labeling
- Very expensive to conduct
- May present more safety concerns than PK studies

Challenges of clinical endpoint studies

- Unknown inter-subject variability within reference population
- Difficulty in achieving consistency between studies
  - study design
  - study population
  - bioequivalence endpoints
- Some products require multiple studies

Dermatologic drugs

- Antifungals and other anti-infectives
  - False negative baseline cultures lead to exclusion of many patients
- Acne products
  - Multiple endpoints
  - Often small effect size and low power to demonstrate BE
- Topical acyclovir
  - Confusion about indications and endpoints